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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,838	12/10/2003	Shaoqing Chen	21101 US2	6737

151 7590 07/01/2005

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EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/732,838	CHEN ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-93* is/are allowed.

6)☒ Claim(s) *94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *15Mar04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 94 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

In making the determination as to whether or not a claimed invention is enabled by the accompanying disclosure, the Office relies on the following factors, promulgated in the decision rendered *In re Wands*:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Each factor will be addressed in the following pages.

(A) Claim 94 is drawn to the treatment of type II (2) diabetes. While this is not extremely broad in scope, it should be noted that the term "type 2 diabetes" generally, refers to a spectrum of severities. Some very severe forms of "type 2 diabetes" might not be clinically distinguishable from type 1 diabetes (insulin-dependent diabetes), while some

extremely mild forms of the disease are more aptly referred to as "insulin resistance" or might even go undiagnosed. The method according to instant claim 94, it is noted, is limited in the dosage amount of the compound according to claim 1 which is administered, namely from 100 to 1,000mg per day.

(B) The invention of claim 94 is a medical treatment method, for type 2 diabetes.

(C) No method whereby type 2 diabetes is treated with a chemical agent that activates the enzyme glucokinase was part of the state of the art when the instant invention was made, although many methods of treating the condition relied on other kinds of drugs, such as those which enhance insulin sensitivity and promote the secretion of insulin. Insulin itself is indicated in the most severe forms of type 2 diabetes. A summary of the state of the art in the treatment of type 2 diabetes, at the time the invention was made, comes from:

> Braunstein, S. "New Developments in Type 2 Diabetes Mellitus: Combination Therapy with a Thiazolidinone" Clinical Therapeutics, vol. 23(7), pages 1895-1917 (2003).

Pages 1896-1901 of Braunstein explain the epidemiology of the disease and summarize complications thereof. At pages 1902-1908, the standard modes of treating the disease are summarized. According to Braunstein, nonpharmacological treatment is the cornerstone of therapy – based on nutrition, weight reduction and exercise. These three aspects of nonpharmacological treatment are essential even when pharmacologic therapy is used (page 1902).

In 2003, medically accepted pharmacologic therapy of type 2 diabetes mellitus was limited to the thiazolidinediones (insulin sensitizers), sulfonylureas (insulin secretagogue), other insulin secretogogues (repaglinide, nateglinide), biguanides

(decrease hepatic glucose output) and α-glucosidase inhibitors (delay carbohydrate absorption from food). Table II summarizes these classes of agent on page 1902 of Braunstein, and a diagram showing the different metabolic targets of these therapies appears on page 1903. At page 1907, it is explained that insulin may be added to other antidiabetics if hyperglycemia is not controlled.

Therapies wherein combinations of thiazolidinediones and other pharmacological agents are used are explained at pages 1908-1909.

So, it is apparent that in 2003, when invention of instant claim 94 was made, no method of treating type 2 diabetes with a glucokinase activator was known to those of ordinary skill in the art (explained in section "D" which follows).

What was known about the therapeutic efficacy of glucokinase activators in 2003 is conveyed by the following articles:

Grimsby et al, "Allosteric Activators of Glucokinase: Potential Role in Diabetes Therapy" Science, vol 301, pages 370-373 (18 July 2003).

and

Couzin, J., Comment on: Science. 2003 Jul. 18; vol. 301, pages 370-373.

The Grimsby et al article is authored by some of the co-inventors named in the instant application. A very closely related glucokinase activator compound is disclosed therein – this compound is similar to the compounds according to claim 1 but lacks the pyridine or pyrazine ring of the compounds according to the invention, instead the compound (dubbed 'RO-28-0450' and its purified *R* and *S* isomers) bears a thiazole ring at that position. Although some anti-diabetic activity is demonstrated in *ob/ob* mice when this compound is orally administered (page 371), the authors state that it is not

ready for general application as a treatment for type 2 diabetes (page 372, last paragraph). Future studies, the authors state, may lead to safe and effective Gluco-Kinase-Activators for clinical trials. One important observation made by the authors of the Grimsby et al reference is that in older *ob/ob* mice that had blood glucose levels near 300mg/dl, the GKAs (glucokinase activators) lost their effectiveness (paragraph bridging pages 371 and 372).

Indeed, a comment on the Grimsby article, appearing in the same issue of the journal *Science*, (authored Couzin, J.) while generally praising the work done by Grimsby et al, express some skepticism about the application of the glucokinase activators in treatment of type 2 diabetes. David Moller, who oversees preclinical diabetes and obesity research at Merck, a competitor to the assignee of the instant application, states that these agents will not likely work in very severe cases of type 2 diabetes. Another potential problem with glucokinase activator therapy, noted in the comment authored by Couzin, is that the agents could lower blood glucose too much, leading to deleterious side effects. Death is sometimes a complication of drug-induced hypoglycemia.

A method of treating type 2 diabetes with a glucokinase activator had only been *suggested* at the time the invention was made.

(D) As the method according to instant claim 94 is a medical treatment method, the level of ordinary skill would be that person who would typically treat the disease being treated. An endocrinologist or internist is the physician who normally treats diabetes

mellitus. The level of ordinary skill with respect to instant claim 94 is therefore, that of an endocrinologist or internist with experience in the field.

(E) As applicants can appreciate, medicine is sometimes predictable, sometimes not. Often, medicine is characterized as an art as much as it is a science. In practice, the physician must often try different therapies on his patient before a satisfactory result is achieved. There is no way to predict exactly how a patient will respond to these different treatments. One thing that can be predicted with some degree of certainty is that a compound according to the invention, a glucokinase activator, is not likely to be an effective treatment for very severe type 2 diabetes, as was evidenced by the comment by diabetes researcher David Moller in the above-cited letter authored by Couzin, commenting on the Grimsby et al article, also cited above.

(F), (G) Applicants have provided some direction, specifically that the preferred dosage range of formula I compounds is 100-1,000mg/day, which dosage range is recited as a limitation in the method of claim 94. This direction consists of section [0125] of the specification, at page 62.

There are no working examples of a method of treating type 2 diabetes, nor any animal model thereof. The *in vivo* examples described in the specification are prophetic. The inventors have described how one would go about determining if the compounds according to formula I have the activity that they purportedly have, but no actual animal data is reported. Pages 195-196 of the specification disclose *in vitro* testing of the compounds from the synthetic examples, and all compounds had a "$SC_{1.5}$" of 100μM or less. The biological or medical significance of this parameter is not readily

apparent, as it is a totally new way of describing pharmacological activity. When the invention was made, there had been as of yet no pharmacological agents for the treatment of type 2 diabetes which are based on *increasing* the activity of a metabolic enzyme.

(H) Since one of ordinary skill in the art would have to pick up the testing and biological characterization of the compounds according to the invention where applicants left off, and also since there are valid concerns about whether all severities of type 2 diabetes would be satisfactorily treated with a compounds according to the invention, it is deemed that for one of ordinary skill in the art to practice the method according to instant claim 94 would require an undue amount of experimentation. Applicants' right to exclude others from practicing the method of claim 94 is not warranted in light of the amount of guidance provided and what was known about the most nearly connected art at the time the invention was made.

Allowable Subject Matter

Claims 1-93 are allowed.

Compounds according to formula I are novel and unobvious over the prior art. The closes prior art comes from applicants' own work – US 6,320,050 (Bizzarro et al) – which shares common inventors with the instant application.

Compounds from Bizzarro et al are like those according to instant claim 1, except Bizzarro et al's compounds either lack a group corresponding to R^4 in instant claim 1, or when such a group is present, it is halogen or carboxyl, neither of which are permitted in

instant claim 1's R^4 (pertinent examples in Bizzarro et al are Example 123, 122, 121, 106 and 105).

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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